Science Translational Medicine Podcast

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Host – Orla Smith

Hello, I'm Orla Smith. Welcome to the *Science Translational Medicine* Podcast for July 13th, 2011. In this show, I will be speaking with Dr. Rino Rappuoli from Novartis about designing a new vaccine to protect against meningococcus B, the bacterial pathogen that causes meningitis.

Pathogens like meningococcus B and HIV show a high degree of antigenic variability that has hampered efforts to develop vaccines against them. For these pathogens, it is not practical to include thousands of variants of an antigen in one vaccine. To tackle this problem for meningococcus B, Rino Rappuoli and his colleagues have taken a structure-based design approach. Using structural information about factor H binding protein, which protects the pathogen from the human immune system, the researchers combined elements of different variants of this protein into one single chimeric antigen. Mice immunized with this chimeric immunogen produced bactericidal antibodies that killed all strains of meningococcus B, suggesting that this vaccine was broadly protective.

Here now is Dr. Rappuoli on the line to discuss the implications of this study.

Interviewer – Orla Smith
Welcome, Dr. Rappuoli, and thanks for joining us.

Interviewee – Rino Rappuoli
So nice to talk to you.

Interviewer – Orla Smith
So why is it so difficult to develop a vaccine against meningococcus B, given that there are vaccines against the other meningococcus serotypes?

Interviewee – Rino Rappuoli
In the case of meningococcus, there are five serogroups that cause disease. They are called A, B, C, Y, and W. For A, C, Y, and W, we can use a capsular polysaccharide, which is a sugar that surrounds the bacteria, to make very effective vaccines, which are already licensed. In the case of meningococcus B, we cannot use the same capsular polysaccharide because the chemical composition is identical to a polysaccharide—a sugar that we have in our body. So our immune system is not able to recognize the meningococcus B polysaccharide as something coming from outside and is not able to

mount an immune response. For this reason, we had to find different ways. And we have been using genomics to find proteins that could be used as vaccine targets.

Interviewer – Orla Smith
So was one of these vaccine targets factor H binding protein?

Interviewee – Rino Rappuoli
One of them was factor H binding protein, which is a an excellent antigen for a vaccine, but even this protein changes from bacterium isolate to other bacterium isolate. And there are thousands of different sequences which are out there of this protein. So we tried to make one protein that would be able to induce immunity against all the others by engineering the protein itself using an approach based on the structure of the protein itself.

Interviewer – Orla Smith
Why is factor H binding protein useful as an antigen?

Interviewee – Rino Rappuoli
Yeah, it's very useful for two reasons. Because in order for the meningococcus to survive in our body, it has to be present on the surface of the bacterium, so it's a very good target. And also, because it's essential for the survival of the bacterium is enough to neutralize the binding of this protein to factor H, and that will also decrease the probability for the bacterium to grow in our body.

Interviewer – Orla Smith
So what is structure-based vaccine design?

Interviewee – Rino Rappuoli
Structure-based approach is quite innovative in designing vaccines. In fact, I think this is the first time that one molecule has been engineered to induce immunity against many different variants. And the reason is that although structural biology has been around for a long time, so far it's been very difficult to make a lot of structures in high-throughput system. Today with the new technologies, it's possible to define a lot of structures and get very quickly the structure of antigens. And, once you have them, now you can use the three-dimensional information to design new antigens. But this way is difficult. One thing that we learned in doing this work is that you cannot just replace one amino acid and you're going to find a final thing. What you need to do is to engineer the entire surface of the molecule if you really want to get a powerful vaccine.

Interviewer – Orla Smith
So what are the four key steps of your vaccine design strategy?

Interviewee – Rino Rappuoli
Well, the first step was to get the structure of the protein. Second was to use biochemical technologies to map in the structure of the protein the amino acids, which were important to induce immunity against the different variants of the protein. Then, once we had mapped the three-dimensional structure, we started to design how we could replace in this structure one of the proteins, the amino acids deriving from these other variants, without destroying the immunogenicity of the first one. And we have been doing this systematically. It's been a long work. We basically divided the protein in many different areas, partially overlapping, and we have engineered each area. And then, once we have engineered that, we have been using the engineered molecules—we did more than 60—and we produced them, we immunized mice, and checked that we're inducing the right immunoresponse. And, at the end, we found that most of them were not optimal, but we found two or three molecules—one of which was very good—which was able to induce immunity against all the variants of the molecule.

Interviewer – Orla Smith
So how did you further test the one or two promising chimeric antigens?

Interviewee – Rino Rappuoli
We basically produced the larger quantities of these new molecules in *E. coli* as recombinant molecules. Then, we purified, immunized mice, and then we tested the sera obtained from the mice for the ability to induce bactericidal killing of the bacteria, which contained different variants of the protein.

Interviewer – Orla Smith
Will your approach be useful for designing vaccines against other pathogens?

Interviewee – Rino Rappuoli
Yeah, I think this new approach where basically structure is used to design new epitopes, and I think this shows that it is possible to engineer in one single molecule many different variants of an antigen. Now, in the case of meningococcus B, variability is big but not huge—HIV, influenza, malaria where the variability might be even larger. But the fact that we've been able to prove that we can do it opens the way to tackle the more difficult pathogens. I believe that this approach will be used more and more in the future and will help to solve some of those very difficult problems.

Interviewer – Orla Smith
Dr. Rappuoli, thank you so much for joining us today and congratulations on a great paper.

Interviewee – Rino Rappuoli
Well, thank you for asking very nice questions. And I hope that this work will be useful [not only] for meningococcus but for many other pathogens.

Host – Orla Smith
That was Rino Rappuoli of Novartis in Siena, Italy. Check out his paper in the July 13th issue of *Science Translational Medicine* by going to our Web site at stm.sciencemag.org.

I'm Orla Smith, thanks for listening!

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